

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Dganit Bar et al.  
Serial No.: Not Yet Known  
Filed: Herewith  
For: INHIBITORS OF SPERMIDINE SYNTHASE FOR THE  
TREATMENT OF OSTEOARTHRITIS AND CARTILAGE  
REHABILITATION

1185 Avenue of the Americas  
New York, New York 10036  
February 24, 2004

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. § 1.56 and § 1.97(a)-(b) applicants would like to direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit A**) and copies of which are attached hereto:

1. U.S. Patent No. 5,514,703, issued May 7, 1996 to Carlson et al. (**Exhibit 1**);
2. Pegg et al. Effects of S-andenosyl-1,3-diamino-3-thioctane on Polyamine Metabolism. Biochem. 1982; 21(20): 5082-5089 (**Exhibit 2**);

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3. Shirahata et al. Effects of Inhibitors of Spermidine Synthase and Spermine Synthase on Polyamine Synthesis in Rat Tissues. Biochem Pharmacol. 1993; 45(9): 1897-1903 (**Exhibit 3**);
4. Slotkin et al.. Polyamides in brain and Heart of the Neonatal Rat: Effects of Inhibitors of Ornithine Decarboxylase and Spermidine Synthase. Life Sci. 1984; 35(10): 1125-1131(**Exhibit 4**);
5. Trentham et al. Autoimmunity to Type II Collagen: An Experimental Model of Arthritis. J. Exp. Med. 1977; 146: 857-868 (**Exhibit 5**);
6. Kong et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. Biochem. Nature. 18 Nov 1999; 402: 304-309 (**Exhibit 6**);
7. Han et al. Effects of Sodium Hyaluronate on Experimental Osteoarthritis in Rabbit Knee Joints. Nayoga J. Med. Sci. 1999; 62(3-4): 115-126 (**Exhibit 7**);
8. Cohen et al. Storing live embryonic and adult human cartilage grafts for transplantation using a joint simulating device. Biomaterials. 2000; 21: 2117-2123 (**Exhibit 8**);
9. Vittur et al. A possible role for polyamines in cartilage in the mechanism of calcification. Biochem Biophys Acta. 19 Mar 1986; 881(1): 38-45 (**Exhibit 9**);
10. Nesher et al. Effect of treatment with methotrexate,

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hydroxychloroquine, and prednisone on lymphocyte polyamine levels in rheumatoid arthritis: Correlation with the clinical response and rheumatoid factor synthesis. Clin. Exp. Rheumatol. Jul-Aug 1997; 15(4): 343-347 (**Exhibit 10**);

11. Wolos et al. Methylacetylenic Putrescine (MAP), an Inhibitor of Polyamine Biosynthesis, Prevents the Development of Collagen-Induced Arthritis. Cell Immunol. Feb 1990; 125(2): 498-507 (**Exhibit 11**);
12. Lakanen et al., Synthesis and Biochemical Evaluation of Adenosylspermidine, a Nucleoside-Polyamine Adduct Inhibitor of Spermidine Synthase. J. Med. Chem. 38:2714-2727 (1995) (**Exhibit 12**); and
13. Liu and Coward, Stereospecific Synthesis of (R)- and (S)-S-Adenosyl-1,8-diamino-3-thioctane, a Potent Inhibitor of Polyamine Biosynthesis. Comparison of Asymmetric Induction vs. Enantiomeric Synthesis. J. Med. Chem. 34:2094-2101 (1991) (**Exhibit 13**).

The above listed references 1, 12, and 13 were cited in a search report issued in connection with an international counterpart of the subject application. A copy of the search report is attached hereto as **Exhibit B**.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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<b>Form PTO-1449</b>		<b>U.S. Department of Commerce Patent and Trademark Office</b>			Atty. Docket No. 66401-AA		Serial No. Not Yet Known						
<b>INFORMATION DISCLOSURE CITATION BY APPLICANT</b> (Use several sheets if necessary)					Applicants Dganit Bar et al.								
					Filing Date February 24, 2004		Group						
<b>U.S. PATENT DOCUMENTS</b>													
Examiner Initial		Document Number				Date	Name	Class	Subclass	Filing Date if Appropriate			
		5	5	1	4	7	0	3	05/07/96	Carlson et al.			
<b>FOREIGN PATENT DOCUMENTS</b>													
		Document Number				Date	Country	Class	Subclass	Translation			
										Yes	No		
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>													
		Pegg et al. Effects of S-adenosyl-1,8-diamino-3-thioctane on Polyamine Metabolism. Biochem. 1982; 21(20): 5082-5089(Exhibit 2);											
		Shirahata et al. Effects of Inhibitors of Spermidine Synthase and Spermine Synthase on Polyamine Synthesis in Rat Tissues. Biochem Pharmacol. 1993; 45(9): 1897-1903 (Exhibit 3);											
		Slotkin et al.. Polyamides in brain and Heart of the Neonatal Rat: Effects of Inhibitors of Ornithine Decarboxylase and Spermidine Synthase. Life Sci. 1984; 35(10): 1125-1131 (Exhibit 4);											
		Trentham et al. Autoimmunity to Type II Collagen: An Experimental Model of Arthritis. J. Exp. Med. 1977; 146: 857-868 et al. CAPRI regulates Ca <sup>2+</sup> -dependent inactivation of the Ras-MAPK pathway. Current Biology. 2001; 11:981-986 (Exhibit 5);											
		Kong et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through steoprotegerin ligand. Biochem. Nature. 18 Nov 1999; 402: 304-309 (Exhibit 6);											
		Han et al. Effects of Sodium Hyaluronate on Experimental Osteoarthritis in Rabbit Knee Joints. Nayoga J. Med. Sci. 1999; 62(3-4): 115-126 (Exhibit 7);											
		Cohen et al. Storing live embryonic and adult human cartilage grafts for transplantation using a joint simulating device. Biomaterials. 2000; 21: 2117-2123 (Exhibit 8);											
		Vittur et al. A possible role for polyamines in cartilage in the mechanism of calcification. Biochem Biophys Acta. 19 Mar 1986; 881(1): 38-45 (Exhibit 9);											
		Nesher et al. Effect of treatment with methotrexate, hydroxychloroquine, and prednisone on lymphocyte polyamine levels in rheumatoid arthritis: Correlation with the clinical response and rheumatoid factor synthesis. Clin. Exp. Rheumatol. Jul-Aug 1997; 15(4): 343-347 (Exhibit 10);											
		Wolos et al. Mathylacetylenic Putrescine (MAP), an Inhibitor of Polyamine Biosynthesis, Prevents the Development of Collagen-Induced Arthritis. Cell Immunol. Feb 1990; 125(2): 498-507 (Exhibit 11);											
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<b>EXAMINER</b>						<b>DATE CONSIDERED</b>							

**\*EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Applicant: Dganit Bar et al.  
 Title: Inhibitors of Spermidine Synthase for  
 Treatment of Osteoarthritis...  
 U.S. Serial No. Not Yet Known  
 Filed: February 24, 2004  
 Exhibit A